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Family Study of Pediatric Patients with Primary Antibody Deficiencies

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ABSTRACT

Common variable immunodeficiency (CVID) and selective IgA deficiency (SIGAD) are the most common primary antibody deficiencies. These two diseases may have coincidence in one family and SIGAD can progress to CVID which suggest common underlying genetic defects between SIGAD and CVID. This study was designed to find the prevalence of multiple cases in families of Iranian patients with CVID or SIGAD.

Serum samples were collected from all available first-degree relatives of 37 patients (23 patients with CVID and 14 with SIGAD) to check the levels of immunoglobulin and their subclasses and detect antibody deficiencies.

First degree family members of 37 patients (106 individuals) were enrolled in this study. Thirty two percent of patients had multiple cases in their families. The frequency of primary antibody deficiency in the first relatives of the patients was estimated to be one per 9 family members. Most of the patients found among family members were siblings of the primary patients. Analysis in SIGAD family members showed that IgG and IgA levels in families with multiple cases were significantly lower than family members without multiple cases (*p* values of 0.048 and 0.021, respectively).

Rate of families with multiple cases in Iran is more than the previous studies in other countries. This rate was not affected by the consanguinity of parents (p=0.081) or immunoglobulin level of the patients. Because of higher risk for the prevalence of these disorders in those with a positive family history of immunodeficiency, family screening programs in the patients with CVID and SIGAD can be suggested to be prioritized..

Keywords: Common variable immunodeficiency; IgA deficiency; Immunologic Deficiency Syndromes; Pedigree

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INTRODUCTION

Common Variable Immunodeficiency (CVID) and Selective IgA deficiency (SIGAD) are the most

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common primary immunodeficiency diseases.[1,2] They are heterogeneous disorders, characterized by decreased serum levels of all or some types of immunoglobulins.[1,3-7] They present mostly with recurrent infections, gastrointestinal disorders, autoimmune diseases, and malignancies.[8-11]

CVID shares many genetic features with SIGAD,[6,12-14] in which the underlying B cell defect and consequently clinical presentations of CVID and SIGAD are partly similar[15] and the linkage of their corresponding genes causes both diseases to occur in the same families.[1,16]

Because of the genetic basis of these diseases, screening the family members of the patients could be an important part of their screening guideline. In addition, due to the high rate of consanguineous marriages in Iran,[17] more families with multiple cases are expected in this region in comparison with western countries. As a result, it is needed to define the frequency of families with multiple cases of these diseases to identify the importance of screening of the family members of the patients.

In this study, we investigated frequency of families with multiple cases in of the Iranian patients with SIGAD in comparison with CVID.

MATERIALS AND METHODS

Family Selection and Study

A descriptive cross-sectional study was performed in the Children's Medical Center, the pediatrics center of excellence in Tehran, Iran during 2007-2011. First-degree relatives of all enrolled patients (23 patients with CVID and 14 with SIGAD), with mean age of 15.9±8.3 years, who were under regular follow-up, were investigated in the study**.** Indeed an uncle of a patient was also enrolled in this study, as of suspicious to an underlying immunodeficiency. The diagnosis of patients with CVID and SIGAD was done based on the criteria of the European Society for Immunodeficiencies (ESID) and Pan American Group for Immunodeficiencies (PAGID) (18). The patients of which their family members were evaluated in this study are labeled as "primary patients". A consanguineous marriage was defined in families in which two partners had at least one ancestor in common, with the ancestor being no more distant than a great-great grandparent (19). If more than one affected patient is found in a family, the term of "multiple cases" family is considered. This study was approved by the Ethics Committee of Tehran University of Medical Sciences.

Immunoglobulin Measurement

After taking an informed consent, blood sampling was performed. Then serum samples were taken to check immunoglobulin and subclasses' levels and detect antibody deficiencies such as SIGAD and CVID. Serum samples were stored at –20ºC and all tests were performed the same day and under similar conditions. Serum immunoglobulin levels were measured, using nephelometry (Minineph human Ig kit, Binding site Ltd, Birmingham, UK). Decreased serum levels of immunoglobulins (IgM, IgG, and IgA) and subclasses considered, when their amounts were at least 2 SD below the reference values for the subject's age.

Statistical Analysis

The Fischer exact test was used for analysis of qualitative data and the independent t test was used for comparison of quantitative ones between two groups such as multiple cases and non-multiple cases families. *p* values less than 0.05 were considered statistically significant.

RESULTS

Families' Characteristics

All available 106 family members (48 males and 58 females), including 35 fathers, 34 mothers, 24 sisters, 12 brothers and only one uncle of 37 patients with CVID and SIGAD, were enrolled in our study. The mean age of enrolled subjects was 33.2±13.9 years. Sixty nine individuals (from 23 families) were relatives of patients with CVID and 37 persons (from 14 families) were relatives of patients with SIGAD. Parents of these families were first cousins in 17 families (46%), and not relevant in 20 families (54%). The Immunological data of studied members is shown in the Table 1.

Multiple Cases

In twelve out of 37 registered patients, more than one cases existed in their families. Among 106 evaluated relatives, 94 individuals (88.7%) were normal and 12 persons (11.3%) showed abnormal immunoglobulin levels in forms of SIGAD, CVID or IgG2 deficiency. The frequency of primary antibody

Table 1. Comparison of immunological data of 37 primary antibody deficiency patients and their 106 relatives.

Topics		N	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)
Primary patients	Common variable immunodeficiency	23	196.9±330.3	16.4±24.9	39.6±43.6
	Selective IgA deficiency	14	1178.9±494.7	3.7±2.9	80.9±45.1
	Total	37	584.7±124.6	11.56±5.7	52.8±28.4
	With multiple cases	12	567.9±72.1	9.9±12.8	58.3±26.4
	Without multiple cases	25	608.8±59.6	14.80±24.3	40.0±29.9
Studied members	Total	106	1224.4±361.2	195.66±117.1	98.6±56.4
	With multiple cases	37	1082.6 ±309.2	121.28±74.0*	84.52±52.8
	Without multiple cases	69	1300.4±410.1	235.6±116.8	106.2±57.1

* p value <0.05 in comparison with remaining patients by independent T student -test statically analysis

deficiency in the first relatives of these patients was estimated to be one patient per 9 family members. Among all 12 multiple-cases families, only one member (except the primary patient) was hospitalized and suffered from severe and chronic infections.

In family study of CVID patients, 8 of 23 families (34.7%) were found as multiple cases, while 8 new patients (5 SIGAD patients, 2 CVID patients and one IgG2 subclass deficiency patient) from 69 studied members (11.5%) were identified. Also, 4 of 14 families (28.5%) of SIGAD were recorded to have multiple cases (4 new patients from 37 studied individuals), which all of these 4 new patients had SIGAD (Table 2).

Siblings and Parents

Most of the patients were found among family members, when sisters or brothers were the primary patients. Therefore, 6 sisters of 24 evaluated sisters (5 of SIGAD patients and one of CVID patients) and 3 of 12 evaluated brothers (one of SIGAD patients and two of CVID patients) were not healthy. In other words, 25% of evaluated brothers and 25% of evaluated sisters showed a primary antibody deficiency disorder. However, only one of 35 evaluated fathers (suffered from SIGAD) and one of 34 mothers (suffered from SIGAD) showed a disease. In this way, 9 out of 36 siblings (25%) and 2 out of 69 parents (2.9%) were found to be patients. Thus, there was a significant effect between relation type and occurrence of primary antibody deficiency (p =0.001).

Interestingly, half of identified patients were sisters of patients with SIGAD; so that half of sisters of patients with SIGAD deficiency showed SIGAD.

Table 2. Characteristics of newly diagnosed patients in the families of known cases.

No.	Family relationship	Consanguine parents	Age (years)	Sex	Diagnosis
1	Father	First cousins	49	Male	IgA deficiency
2	Mother	No	34	Female	IgA deficiency
3	Brother	First cousins	13	Male	Common variable immunodeficiency
4	Brother	First cousins	6	Male	Common variable immunodeficiency
5	Brother	First cousins	6	Male	IgA deficiency
6	Sister	First cousins	18	Female	IgA deficiency
7	Sister	No	13	Female	IgA deficiency
8	Sister	First cousins	21	Female	IgA deficiency
9	Sister	First cousins	12	Female	IgA deficiency
10	Sister	No	5	Female	IgA deficiency
11	Sister	No	6	Female	IgA deficiency
12	Uncle	No	25	Male	IgG2 subclass deficiency

Table 3. Comparison of immunological data between multiple case and non multiple cases of 23 CVID and 14 SIGAD patients.

Topics		N	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)
Primary CVID patients	Without multiple cases	15	249.20±152.7	20.47±14.7	38.73±21.6
	With multiple cases	8	153.0±93.2	12.38±5.7	36.25±19.3
	p value		*0.23*	*0.09*	*0.35*
Primary SIGAD patients	Without multiple cases	10	1146.30±426.7	6.30±3.2	80.40±39.3
	With multiple cases	4	1397.75±654.1	5.0±4.1	102.25±45.6
	p value		*0.54*	*0.461*	*0.776*

Table 4. Comparison of immunological data between multiple case and non multiple cases of 37 relatives of CVID patients and 69 relatives of SIGAD patients.

Topics		N	IgG (mg/dL)	IgA (mg/dL)	IgM (mg/dL)
Family members of CVID patients	Without multiple cases	24	1192.67±435.7	193.83±73.4	108.62±58.6
	With multiple cases	13	1161.22±519.6	128.57±73.2	92.57±43.8
	p value		*0.317*	*0.567*	*0.446*
Family members of SIGAD patients	Without multiple cases	45	1357.91±662.8	257.8±117.2	104.89±62.7
	With multiple cases	24	1040.0±509.7	117.33±49.3	80.17±53.7
	p value		*0.048**	*0.021**	*0.740*

This rate revealed no significant difference between families with relevant and non relevant parents. Thus, the effect of being sibling or parent on being a patient was assessed in subgroups based on primary patient's disease.

In subgroup analysis of primary patients with SIGAD, 3 out of 10 siblings (30%) and 1 out of 26 parents (3.8%) were found to be patient (*p* value=0.02). Also, in subgroup analysis of primary patients with CVID, 7 out of 26 siblings (26.9%) and 1 out of 43 parents (2.3%) were found to be patient (*p* =0.01).

Parental Consanguinity

Eight of 12 multiple cases families (66.6%) revealed parental consanguinity, which is higher, but not significantly than non-multiple case families (41%; *p* =0.081). It showed a trend toward the higher probability of being a multiple cases family in those that parents are consanguine.

Immunoglobulin Levels

Mean IgA level of primary patients who were in a multiple cases family was lower than IgA level of other primary patients (9.9±12.8 *vs.* 14.8±24.3 mg/dL; *p* =0.056). The difference of IgG levels (567.9±720.2 *vs.* 608.0±598.6 mg/dL) and IgM levels (58.3±46.5 *vs.* 55.4±49.9 mg/dL) were not significant between the two groups ($p > 0.05$). Other subgroups immunological comparisons are presented in the Tables 2 and 3.

When analysis was performed separately among SIGAD family members, mean IgG (1040.0±509.7 *vs.* 1357.9±662.8 mg/dL; *p* value=0.048) and IgA (257.8±117.2 *vs.* 117.3±49.3 mg/dL; *p* =0.021) levels of family with multiple cases were significantly less than family members without multiple cases (Table 3).

Multiple cases showed significantly higher rate of severe switched memory B cells defects (CD19+CD27+IgD cells <0.4 ng/mL) (20) in comparison with patients without multiple cases in their family members (7 of 12 *vs.* 3 of 25; *p*=0.006).

There was not any difference between multiple cases groups of patients and non multiple cases on types of phenotyping (21) (infectious only, poly-lymphocytic infiltration, autoimmunity, enteropaty and malignancy) and age of diagnosis (pediatrics or adults) of patients.

DISCUSSION

Common variable immunodeficiency and SIGAD are the most common and symptomatic primary immunodeficiency diseases.[1] Because of genetic differences within different ethnicities, it is expected to have different rates of familial inheritance and

multiple cases families in different regions of the world. Overall, familial inheritance of either SIGAD or CVID occurs in about 20% of the cases.[8] The frequency of primary antibody deficiency in the family members of patients is about 11,300/100,000 which is much higher than the prevalence in general population (2/100,000).[6]

Although our preliminary study showed a rate of 41.7% for multiple cases in CVID patients' families,[22] this study revealed 32.4% of families were multiple cases, when both CVID and SIGAD were considered. This high rate of familial clustering of CVID and SIGAD could be partly due to genetic difference of different ethnicities. Moreover, in 43.2% of families, parents were consanguine. Regarding the fact that genetic diseases such as SIGAD and CVID are more common in families with consanguine parents, effect of consanguinity of parents on familial clustering of these diseases was also evaluated in this study which was not significant, but there was a trend toward the higher probability of being a multiple cases family in those with consanguine parents.

According to the results of this study, the risk of being a patient was significantly more among siblings than parents. It is in concordance with previous studies which showed a high relative risk of being a patient for siblings of patients with CVID or SIGAD (8). Besides in our study half of identified patients were sisters of patients with SIGAD and half of the sisters of patients with SIGAD had SIGAD. Thus, it could be suggested to perform screening programs primarily for siblings of patients.

It is proposed that a gradual decline of IgG levels causes CVID which develop later in life as a more severe manifestation of a common, complex genetic defect, most likely involving immunoglobulin class switching. This is supported by the finding that in multiple-cases families CVID is usually present in the parents and SIGAD is present in children.[23] However, in this study, all the three identified cases of CVID were siblings of primary patients and all the patients' parents showed SIGAD.

In conclusion, the rate of multiple cases families in our study was 32.4%, which is more than studies in other countries. Besides due to the higher risk of being a patient, it might be beneficial to prioritize the familial screening programs for the patients with CVID and SIGAD for siblings of patients.

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